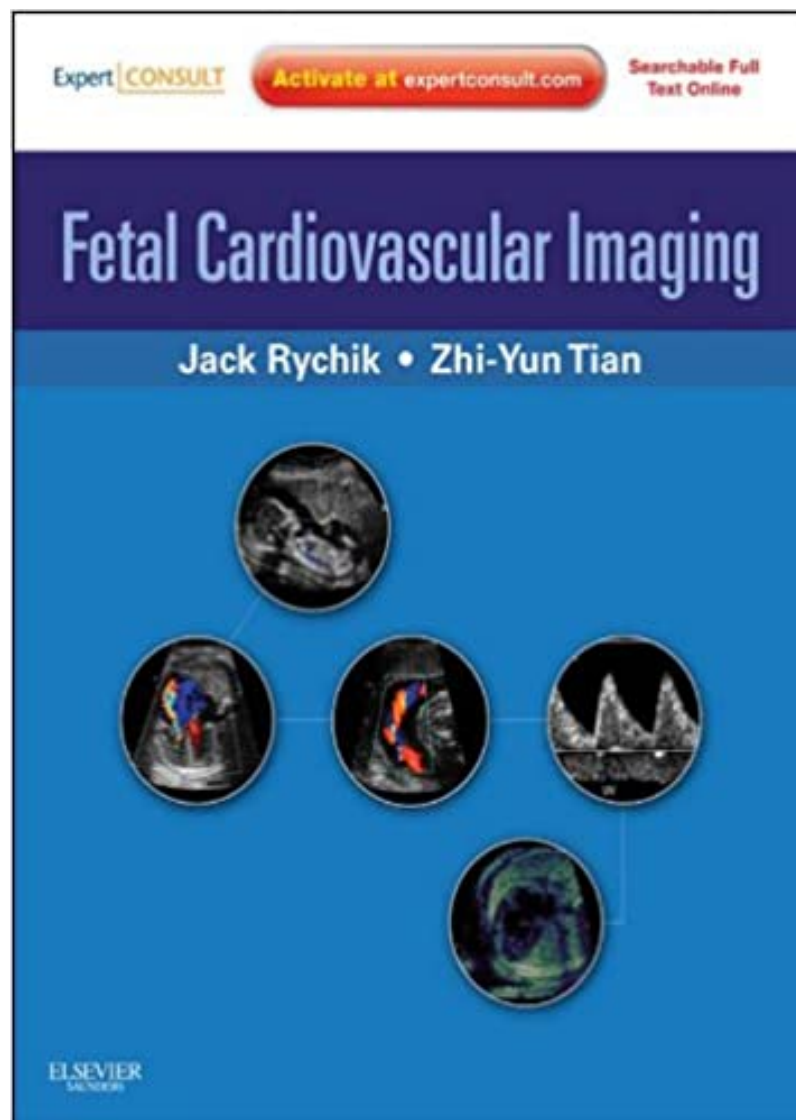


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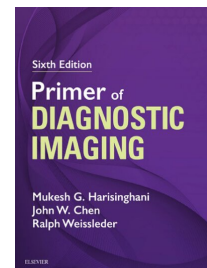


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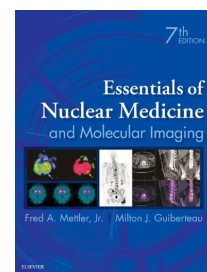
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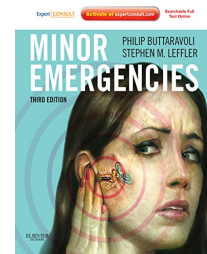
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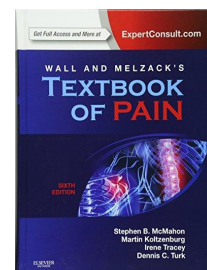
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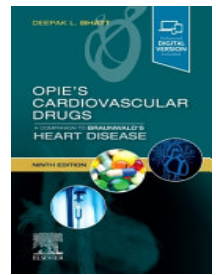
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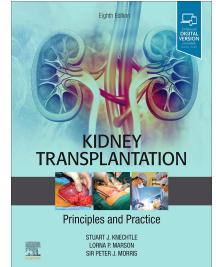
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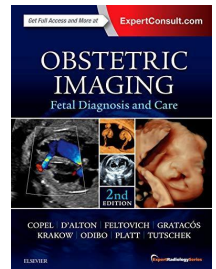
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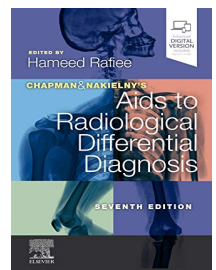
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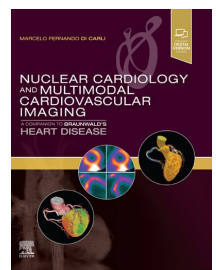
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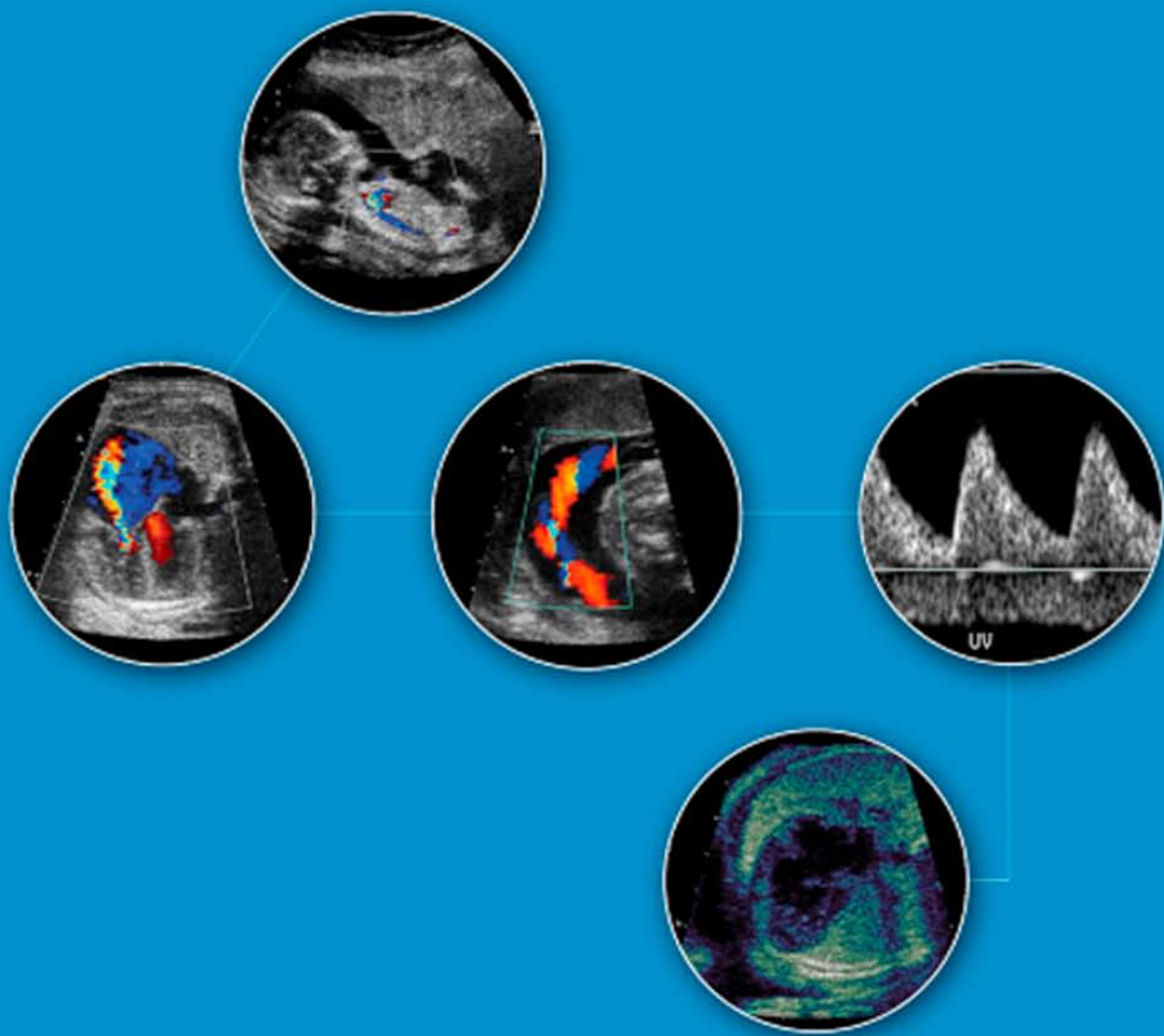
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Fetal Cardiovascular Imaging

Jack Rychik • Zhi-Yun Tian



Preface

Fetal Cardiovascular Imaging: A Disease-Based Approach is a combination textbook with still images and an accompanying library of videos. Whereas a number of texts exist on the “how-to” and technical aspects of fetal echocardiography, our goals were to adequately cover these areas, but focus more so on the variety of disorders and conditions that affect the fetal cardiovascular system, with emphasis on the imaging specifics particular to the condition of interest.

How can the printed pages of a book adequately inform on a complex diagnostic process that involves the imaging of a moving, beating structure, that of the fetal heart? The answer is simply that a book of text alone is inadequate to achieve this task. In the year 2011, technologies for imparting knowledge allow for the combination of visual media in order to best convey the optimal informative and educational experience. This book was therefore created as an equal partner and complement to an imaging library with an array of imaging videos available for your review. The chapters are organized as individual anomalies, with broad coverage of primary congenital heart defects and other conditions that secondarily affect the fetal cardiovascular system. Each chapter is further divided into sections on genetics, prenatal diagnosis, prenatal pathophysiology, prenatal management, postnatal pathophysiology and management, and finally, prognosis and outcome. In this manner a comprehensive overview from diagnosis, to care, to outcome, can be gleaned for a variety of fetal cardiovascular conditions.

This book and video library was initiated by the realization that over the past few years, we had collected a

wealth and breadth of fetal cardiovascular images covering a wide range of anomalies. Sharing this library of images beyond our walls was of utmost importance. Each of our chapters includes a number of case examples of real patients we have seen, with demonstration of various points of importance and interest. The ideal experience for this educational encounter is an initial reading of the text and then a visit to the images to witness the heart in motion. Each of the conditions can be systematically studied in this manner. Alternatively, the image library can act as a reference with which to compare unknowns in the real clinical world, in order to help identify and correctly diagnose challenging patients. When faced with a set of unknown images in the clinic setting, a look at our image library may confirm a particular diagnosis or send the practitioner off to the next anomaly on the differential diagnosis list. If the images match up, then a look back to the text can inform on the physiology, management and counseling appropriate for the condition at hand.

Although derived from our pediatric cardiology based practice, this book and imaging library is designed with a multidisciplinary audience in mind. Practitioners of maternal fetal medicine, obstetrics, pediatric cardiology, medical sonography, perinatology, neonatology and radiology all have a growing interest in fetal medicine with focus on the fetal heart and vasculature. We hope this book will be of use to the greater community at large sharing in the care for the unborn child.

Jack Rychik
Zhiyun Tian

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Acknowledgments

This project was born of an idea to fill a void and provide a reliable source of imaging knowledge in the developing discipline of cardiovascular care before birth. Dr. Tian and I first discussed the notion of a book and took up this challenge a while back, longer than either of us would like to admit. Finally, here it is. No endeavor, certainly not a book and video imaging project of this scope, can come to fruition by the energies of the creators and editors alone, no matter how motivated. There are a number of people to thank who have encouraged and supported this project along the way, facilitating its completion.

My wife Susan and my daughters Jordana, Leora, and Natali have tolerated countless hours, nights, weekends and then weeks of separation from me as I worked on this project. Words cannot express how grateful I am for your sacrifices and steadfast love. You are my facilitators, my enablers, and without your support this endeavor would never be possible.

I have had the unique opportunity to learn about congenital heart disease from an incredible group of brilliant and provocative thinkers. Alvin Chin, John Murphy, William Norwood, and Marshall Jacobs provided me with a strong foundation of knowledge. I thank them for instilling in me an appreciation for the importance of rigorous logic as the source for all good clinical care.

Natasha Andjelkovic and Julia Bartz of Elsevier were instrumental in encouraging me to keep moving forward, and I thank them for their advice and patience. My Division of Cardiology Chief, Dr. Robert Shaddy, and Department of Pediatrics Chair, Dr. Alan Cohen, saw in me the potential to complete this task, if only I could focus more fully on the project. I am forever indebted for their support of my taking a brief sabbatical in Israel, which allowed me to re-energize and complete this task. While

in Israel, I also had the fortunate opportunity to develop a professional relationship with Dr. Simcha Yagel of Hadassah Hospital, an endlessly energetic maternal fetal medicine specialist whose brilliance and gracious hospitality were instrumental at a critical time of writing.

I am fortunate to work with an amazingly talented and dedicated group of individuals. In addition to Dr. Zhiyun Tian, co-editor of this project, Peggy McCann, RCDS, and Debra Soffer, RCDS, are personally responsible for the high-quality echocardiograms that comprise this effort. It is primarily their three pairs of incredibly gifted hands at the echo machine that fashioned these images. Denise Donaghue, RN, and I have dedicated the past 10 years of our careers to building the Fetal Heart Program at The Children's Hospital of Philadelphia, a task of which we are immensely proud. Without Denise's vision, dedication, and incredible skill, we would not have had the program and clinical experiences with which to generate the knowledge for this book. Nurse coordinator Jill Combs, RN, and social workers Lucia Figueroa and Jennifer Diem-Inglis have been steadfastly amazing at coordinating compassionate care for our pregnant mothers, this at what can be considered one of the most traumatic of life experiences—uncovering the presence of a serious fetal anomaly. It is this synthesis of skilled imaging, coordination of care, and compassionate family centered counseling that has created our unique service. To all of the members of the Fetal Heart Program, thank you for your work—you make me proud to be a part of your team.

Finally, I must thank the countless patients and families who have sought our opinions and advice over the years and have entrusted us with their care. I have learned from each and every one of you.

Jack Rychik

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Acknowledgments

For the past 2 decades, I have had the privilege of working in the Fetal Heart Program at The Children's Hospital of Philadelphia. Over the years, we have carefully accumulated a large number of cases and always knew we would someday share this image collection with our medical community. Thus, it is extremely gratifying that Dr. Jack Rychik and I, with the support of our many colleagues and Elsevier, have produced this book and imaging library.

I am indebted to many for helping this dream come true.

First, I would like to thank my family: My parents raised me to be a strong and giving person and always told me "love what you do and be the best." My four brothers have unconditionally supported and encouraged me to set and achieve higher standards.

I would like to thank my birth country, China, where I received an excellent education, enabling me to lay a firm foundation for my career today.

I wish to express my gratitude to my teachers and mentors in China and the United States. Your guidance and support for me, with your knowledge and experience, has made it possible for me to be successful in this field.

I would also like to thank The Children's Hospital of Philadelphia, an amazing organization that has given me

a most incredible opportunity to grow and advance my skills. I want to thank the hospital leadership and colleagues for their dedicated support during the past 2 decades. I deeply love my work environment and my office family members, who have always provided me with a nurturing environment.

To my students, the young physicians from China, you have given your unselfish support to this effort. I will always remember those evenings and weekends you dedicated to helping me edit our images, and all of the happy times we spent together.

Most important, my grateful thanks to all of the patients, mothers, and babies (before you were born) that I have served for the last 20 years. Each of you gave me the privilege to help you through the use of ultrasound, to learn from your imaging, to understand your heart and to find answers to difficult questions before you were born. Without you, this book would not be possible.

Finally, I thank my husband Michael, for his love and support, and my son Steven, who followed me into medicine and has made me proud and happy every day.

Zhiyun Tian

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Foreword

During the past 2 decades, we have witnessed significant developments in the diagnosis and treatment of fetal anatomic and genetic abnormalities. The prenatal detection and serial sonographic, echocardiographic, and MRI study of fetuses with anatomic malformations has permitted delineation of the natural history of these lesions, definition of the pathophysiologic features that affect clinical outcome, and formulation of management based on prognosis. This is true for fetuses with cardiac and non-cardiac disease. The diagnosis and treatment of human fetal defects has also evolved rapidly as a result of a better understanding of fetal pathophysiology derived from animal models. Most fetal anomalies that are correctable and can be diagnosed in utero are best managed by appropriate medical and surgical therapy after maternal transport and planned delivery at term. Prenatal diagnosis may also influence the timing or mode of delivery and in some cases may lead to elective termination of the pregnancy. In some highly selected circumstances, various forms of in utero therapy are now available. The crucial concept in this burgeoning field is that accurate diagnosis is imperative for effective family counseling, pregnancy management, and therapy. This textbook entitled *Fetal Cardiovascular Imaging: A Disease-Based Approach* beautifully describes all of the hallmarks of prenatally diagnosed cardiovascular disease.

Since the most severely affected fetuses often die in utero or shortly after birth, a fetal surgical approach has been defined for highly selected fetuses with thoracic masses or sacrococcygeal teratoma associated with fetal hydrops. Fetal cardiovascular pathophysiology is paramount in these conditions. The fetal surgical approach to in utero myelomeningocele repair has been developed as an approach to a potentially devastating but non-life-threatening malformation. The field has evolved to the point where an NIH-sponsored prospective randomized clinical trial is now comparing fetal repair to postnatal repair of myelomeningocele. This trial provides the groundwork for future critical testing of fetal therapeutic procedures.

Much work is being performed on the perioperative anesthetic management of the fetal surgery patient. Anesthetic considerations include the physiologic changes of pregnancy, preterm labor, the effects of tocolytic drugs, maternal and fetal anesthesia, and postoperative analgesia. The effect of these changes on the cardiovascular status of the fetus is important and is the principal reason

why fetal echocardiographic monitoring is now used on a routine basis for all of our fetal surgical procedures.

Minimally invasive or fetoscopic approaches will have an increasing therapeutic role in the future as indications, instrumentation, and techniques are refined. Fetoscopic laser ablation of abnormal shared placental vessels in Twin-Twin Transfusion Syndrome (TTTS) is now established therapy, although patient selection criteria—particularly related to the cardiovascular status in TTTS—need further study. There is now a very large clinical experience with percutaneous shunt procedures for lower urinary tract obstruction and for thoracic diseases associated with fetal hydrops such as congenital cystic adenomatoid malformation of the lung and fetal hydrothorax. Percutaneous approaches in utero are now being evaluated in cases of critical aortic stenosis with evolving hypoplastic left heart syndrome in an effort to maintain two ventricle physiology. Percutaneous approaches are also being used to perform an atrial septostomy in cases of hypoplastic heart syndrome with intact atrial septum in an attempt to avert the pulmonary vasculopathy seen in this condition.

The Ex Utero Intrapartum Therapy (EXIT) procedure for intrinsic and extrinsic causes of fetal airway obstruction is now well established and has been used at many medical centers by multidisciplinary teams. This approach provides time to perform procedures such as direct laryngoscopy, bronchoscopy, or tracheostomy to secure the fetal airway, thereby converting an emergent airway crisis into a controlled situation during birth. Similarly, we now use the Immediate Postpartum Access to Cardiac Therapy (IMPACT) procedure to specially deliver prenatally diagnosed cardiac patients who need immediate postnatal therapy.

In the future, in utero hematopoietic stem cell transplantation will be a promising approach for treatment of a potentially large number of fetuses affected by congenital hematologic and immunologic disorders. Advances in gene transfer technology and prenatal diagnosis prompt consideration of a fetal gene therapy approach to correct genetic disease. For many genetic diseases, the fetal period may be the only time in which genetic intervention can prevent disease manifestations. It is conceivable that these approaches may be used to benefit fetuses with cardiovascular disease.

The contributors to this book, under the editorial leadership of Doctors Rychik and Tian, are mostly current

members of the Cardiac Center faculty at The Children's Hospital of Philadelphia. Thus, the presentations reflect the philosophy of one center, gleaned from more than 2 decades of experience. This book is directed toward fetal and pediatric cardiologists, pediatric cardiac surgeons, pediatric cardiac anesthesiologists, perinatologists, echocardiographers, neonatologists, geneticists, pediatricians, and nurses who are vital components of a multidisciplinary team that manages the fetus with a cardiac defect.

With continuing research efforts and clinical application, the care of the fetal cardiac patient will continue to improve.

N. Scott Adzick, MD

Surgeon-in-Chief

The Children's Hospital of Philadelphia

Director, Center for Fetal Diagnosis and Treatment

Philadelphia, Pennsylvania

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Introduction

1

The Fetal Circulation

Max Godfrey and Jack Rychik

Introduction
Ductus Venosus, Hepatic Circulation, and Inferior Vena Cava
Foramen Ovale
Ductus Arteriosus
Aortic Isthmus
Pulmonary Trunk and Right-sided Dominance
Placental Development and Physiology

Introduction

We begin our examination of the normal fetal circulation with a description of the anatomical pathways involved (Figure 1-1).

Oxygenated blood leaves the placenta via the umbilical vein (UV). From the UV, between 20% and 50% of the blood flows into the ductus venosus (DV), which joins the inferior vena cava (IVC) shortly before it enters the floor of the right atrium (RA). The rest of the UV blood perfuses the liver, and then rejoins the IVC circulation via the hepatic veins. Blood within the IVC that originated from the DV is mainly streamed preferentially through the foramen ovale (FO) into the left atrium (LA), through the mitral valve (MV) into the left ventricle (LV), and then

out through the aortic valve (AoV) and into the ascending aorta (AAo). This blood then flows across the aortic arch, where it provides relatively oxygenated blood to the head, myocardium, and upper body via the coronary, carotid, and subclavian arteries, with a small portion continuing on via the aortic isthmus to the descending aorta (DAo).

Deoxygenated blood from the superior vena cava (SVC), together with the majority of non-DV-originating blood in the IVC flows into the RA, through the tricuspid valve (TV) into the right ventricle (RV) and out through the pulmonic valve (PV) into the pulmonary artery (PA). From the PA, approximately 20% of the blood flows to the lungs, with the remainder flowing through the ductus arteriosus (DA) to join the DAo, where it makes up the majority of the flow. The blood flowing through the DAo supplies the internal organs and the lower body, as well

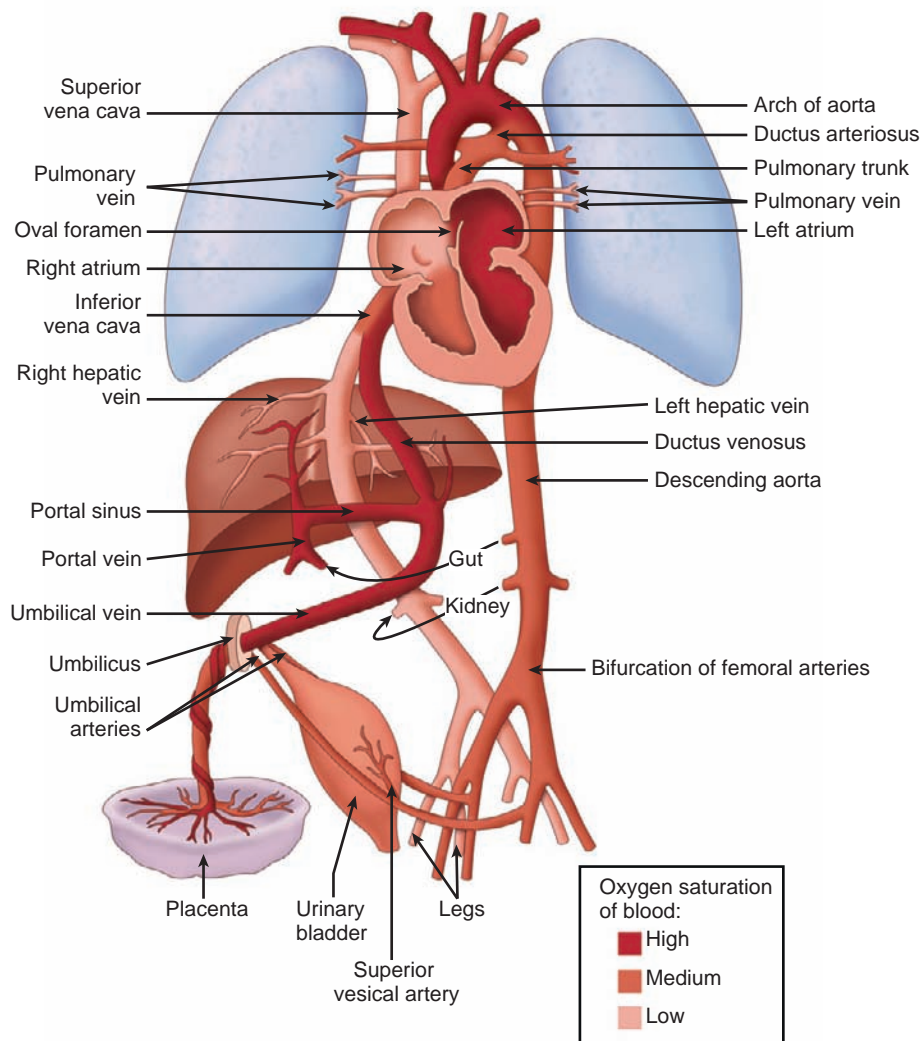


Figure 1-1. The fetal circulation demonstrating flow pathways from placenta to fetus. *Shadings* indicate the various oxygen saturations. The most highly oxygenated blood returns via the umbilical vein and is preferentially directed across the foramen ovale to the left atrium and left ventricle. Relatively deoxygenated blood mixes in the right atrium and moderately saturated blood is then ejected out of the right ventricle across the ductus arteriosus to the descending aorta. The umbilical arteries arise from the internal iliac arteries and deliver blood to the placenta to replenish oxygen supplies.

as the two umbilical arteries that return blood to the placental circulation. Thus, the fetal circulation is essentially a parallel circulation with three circulatory “shunts”: the DV, the FO, and the DA. This circulatory design has a targeted goal—the brain, coronary circulation, and upper body are essentially supplied with relatively oxygenated blood via the LV, whereas the lower body receives mainly deoxygenated blood via the RV.

The majority of foundational research into the fetal circulation has been carried out on fetal sheep, which have the advantage of being large mammals, yet with a gestational duration about half the length of humans. More recent research based on ultrasonographic and Doppler studies has highlighted important differences between humans and sheep. This is perhaps not surprising because sheep fetuses have two UVs, a faster growth rate, a higher body temperature, a lower hemoglobin, a smaller brain, a differently positioned liver, and a longer intrathoracic IVC.¹

Ductus Venosus, Hepatic Circulation, and Inferior Vena Cava

The DV is a small vessel that has been variously described as being shaped like a trumpet or an hourglass. It connects the UV to the IVC as it enters the RA, at the confluence with the hepatic veins (Figure 1-2). Early animal studies indicated that 50% of UV blood flow was channeled into the DV,² with the amount of shunt through the DV proportional to the UV flow,³ implying a significant physiological role for this pathway. However, more recent studies of human fetuses using noninvasive ultrasonographic techniques have shown that the amount shunted through the DV is less and, moreover, that there is a decrease in shunting throughout gestation (i.e., more UV blood traversing the liver with later gestation). Kiserud and coworkers⁴ demonstrated that the percentage of blood shunted through the DV decreases from approximately 30% at 18 to 19 weeks' gestation to approximately 20% at week 30, although with wide variations between subjects. Bellotti and colleagues⁵ found that the percentage shunted was approximately 40% at 20 weeks, decreasing to approximately 15% at term. Work based on mathematical impedance modeling of the hepatic venous network suggests that the shunt decreases from 50% at 20 weeks to 20% at term.⁶ Interestingly, the data suggesting a shunt of 50% from the original seminal study of Rudolph and Heymann in 1967² do not appear to be controlled for gestational age. Thus, there may be less conflict between the animal and the human data than has been suggested. As a greater percentage of UV return is directed through the liver with later gestation, it raises the speculation of the liver playing an important role in third-trimester fetal maturation and growth through the release of proteins and mediators. The role of the liver as “gate-keeper” to placental venous

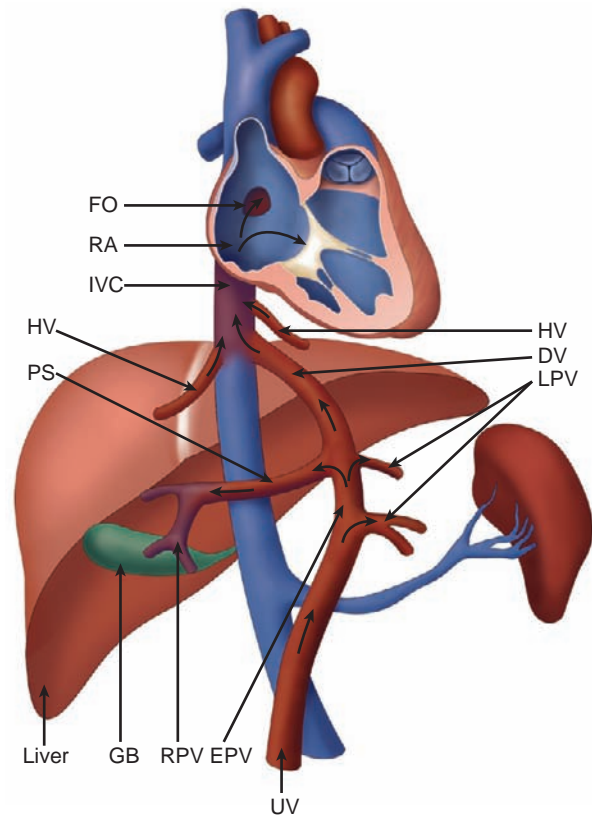


Figure 1-2. Schematic representation of the fetal umbilical, portal, and hepatic circulations. The arrows indicate the direction of blood flow and the color shows the degree of oxygen content (red = high; blue = low). DV, ductus venosus; EPV, extrahepatic portal vein; FO, foramen ovale; GB, gallbladder; HV, hepatic vein; IVC, inferior vena cava; LPV, left portal vein; PS, portal sinus; RA, right atrium; RPV, right portal vein; UV, umbilical vein.

return in the growing fetus is a fascinating one, and still poorly understood.

Within the IVC entry site at the floor of the RA, the column of blood originating from the DV is preferentially streamed across the FO into the LA,⁷ and the remainder enters the RA and crosses the TV. The mechanism by which this occurs is likely related to the complex geometry of the vessels as they enter the RA floor; the phenomenon can be demonstrated on Doppler color flow mapping.⁸ In sheep, there are valvelike structures at the opening of the DV and left hepatic vein that may physically direct the different flows from within the IVC.⁸ However, these structures do not appear to exist in the same way in the human fetus.⁹ Kiserud and Acharya¹⁰ suggest that the rapid increase in velocity of the blood within the DV, caused by the pressure gradient, means that the blood column originating from the DV has the highest kinetic energy; thus, it is this blood that opens the FO valve and enters the LA.

A related controversy concerns the presence of a sphincter mechanism within the DV by which flow may be increased or decreased.¹¹ It has been demonstrated, in both animal and human models, that the flow through

the DV is increased in certain conditions such as hypovolemia¹² and hypoxemia.¹³ Some studies have favored the presence of a discrete sphincter mechanism that controls the caliber of the DV,^{8,14} whereas others propose that the entire vessel is tonically controlled by neurohumoral mechanisms.^{15,16} Alternatively, a drop in resistance to flow through a relaxation of the portal vascular system may direct blood away from the DV. This notion is supported by the finding of a greater degree of smooth muscle in the walls of the fetal portal venous system than in the DV.

Blood from the left hepatic vein is also shunted preferentially through the FO, owing to the position of its entry into the IVC just under the eustachian valve.¹⁷ In fact, the liver, despite its high metabolic activity in the fetus, extracts relatively little oxygen (10–15%¹⁸), such that hepatic venous blood is fairly well oxygenated and, thus, potentially contributes to the highly oxygenated blood-streaming phenomenon within the fetal heart.

Foramen Ovale

In the postnatal human infant, the FO is commonly thought of as being a connection between the two atria, causing shunts from one side to the other. It has also been described as such in the fetus.¹⁹ However, it is contended that in the fetus, the anatomical and functional arrangement is different. The FO flap and the crista dividens of the interatrial septum act as a “valve,” directing the stream of blood from the IVC, which enters essentially between the two atria from below. The stream of blood is divided due to position, direction, and velocity, with DV and left hepatic venous blood directed to the left atrium, while abdominal IVC blood is directed to the RA.¹⁷ Changes in pressure on either side will change the balance of flow, and this can have far-reaching consequences for the development of the fetal heart. For example, in aortic stenosis, left atrial pressure is elevated thereby increasing shunting of blood to the RA, which by neglecting the LA, may eventually lead to left-sided hypoplasia,^{20,21} although the causal chain of events is very much controversial.²² Experimental models have shown that normal flow distributions within the developing heart may be critical for normal cardiac morphogenesis.^{23,24}

Ductus Arteriosus

The DA is a large vessel with muscular walls, which connects the pulmonary trunk and aorta. The systolic flow within the DA has the highest velocity of all the fetal cardiovascular system, and the velocity increases with increasing gestational age.²⁵ The human DA shunts an estimated 78% of the right ventricular output, or 46% of the combined cardiac output (CCO),²⁶ away from the lungs to join the DAo and perfuse the lower body. These figures are slightly lower than in sheep models, which suggest that the DA carries 88% of the right ventricular output and 58% of the CCO.⁹ The patency of the DA

depends on levels of circulating prostaglandin E₂ (PGE₂),²⁷ but the flow through the DA is dependent on the resistance of the pulmonary vasculature. The pulmonary vasculature undergoes changes during the third trimester of gestation such that increases in partial pressure of oxygen (PO₂) cause resistance to decrease and, therefore, flow through the DA to change accordingly.²⁸ This mimics the physiological processes that take place after birth with the onset of breathing and can theoretically be used as an in utero test for fetal pulmonary vascular development such as in conditions of congenital heart disease or pulmonary hypoplasia.

The sensitivity of the DA to PGE₂ in utero has clinical significance, because maternal administration of PGE₂ inhibitors such as indomethacin can cause the DA to close with catastrophic consequences.²⁹ The response to indomethacin is thought to be potentiated by stress, and intraoperative echocardiography demonstrates that indomethacin used in fetal surgery induces more potent constriction of the DA.³⁰ Interestingly, there seems to be some “physiological” constriction of the DA as gestation proceeds toward term, which may explain the increased velocity that is seen in the DA relative to the PA.²⁵ Because the lungs represent a major site of PGE₂ metabolism,³¹ it would seem plausible that this constriction of the DA is due to increased prostaglandin degradation because pulmonary perfusion increases toward the end of gestation.³²

Aortic Isthmus

The isthmus of the aorta (the section of the aortic arch between the take-off of the left subclavian artery and the insertion of the DA) represents a watershed region between the aortic arch, which transmits relatively well oxygenated blood to the head and upper body, and the DA, which transmits relatively deoxygenated blood to the lower body.³³ The isthmus may also represent a functional division between these two arterial circuits, because noradrenaline and acetylcholine injected into either side of the isthmus in the fetal lamb can be demonstrated to affect only that side for at least a few heartbeats.³⁴ Animal studies have shown that, under physiological conditions, only 10% to 15% of the CCO is transmitted through the isthmus³⁴ because the majority of blood in the ascending aorta is distributed to the myocardium, head, and upper limbs via the coronary, carotid, and subclavian arteries. One of the most important hemodynamic factors influencing the direction of flow through the isthmus is the relative resistances of the cerebral and placental circulations. If the placental resistance (which is normally very low) increases sufficiently, the two circuits (upper and lower body) can be separated, with blood ejected from the LV perfusing the heart and upper body only, with negligible forward flow (because the placenta is no longer the site of lowest vascular resistance). Meanwhile, the RV perfuses the lower body exclusively. As placental

resistance progressively increases, retrograde flow can be detected in the isthmus.³³ Indeed, the isthmus represents an example of the plasticity of the fetal circulation to adapt to varying circumstances. For example, as in cases of reduced left ventricular output, DA blood flows retrograde through the isthmus to supply the AAO and aortic arch.¹⁰

Pulmonary Trunk and Right-sided Dominance

Experiments in fetal lambs have shown that of the CCO, 60% to 65% is ejected from the RV and 35% to 40% from the LV,³⁴ while of the blood ejected from the RV, approximately 90% is shunted through the DA, with only approximately 10% (i.e., ~3.5% of CCO) reaching the lungs. The proportion ejected through the branch pulmonary arteries has been demonstrated to increase throughout gestation, almost doubling from the second third of pregnancy to near term.³⁵

Studies on human fetuses, using echocardiographic techniques to measure flow volumes, have found a wide variety of values for these ratios. Rasanen and associates³² found that the proportion of CCO perfusing the lungs in the human fetus at 20 weeks' gestation was 13%, increasing to 25% at 30 weeks, and remaining fairly constant from then on. That study, using echocardiography, found that the ratio of proportion of CCO ejected by each ventricle (RV:LV) was 53:47 at 20 weeks, increasing to a maximum of 60:40 at term—that is, slightly less than the results from animal studies. Conversely, St. John Sutton and coworkers³⁶ reported a mean pulmonary blood flow that comprised 22% of CCO, with a RV:LV ratio of 52:48, which remained unchanged throughout the second half of gestation. Mielke and Benda²⁶ reported that the RV:LV ratio was 59:41, the proportion of RV flow reaching the branch PAs was approximately 20%, and the pulmonary flow represented 11% of CCO. None of these values was found to change significantly throughout gestation. Table 1-1 summarizes these results.

Researchers have consistently found that there is a significant right ventricular dominance in human fetuses and that this dominance is less prominent than in animal models.³⁷ There are a number of plausible explanations;

however, the reason for this right-sided dominance in cardiac output is unclear. Rudolph³⁴ hypothesizes that it is due to the increased afterload faced by the LV. This afterload is caused by the narrowing of the aorta at its isthmus, which causes the cross-sectional area to be reduced by half. Alternatively, the RV preferentially perfuses the placenta, which is an organ in demand of significant flow throughout gestation. These demands upon the RV lead to a particular ventricular geometry, which is abandoned once the RV transitions to the role of a low-pressure pulmonary ventricle after birth.

The reduced right ventricular dominance found in human fetuses relative to animals is suggested to be due to an increased brain volume, which necessitates increased blood flow. The blood flow to the brain is supplied by the LV, which therefore needs to provide a relatively higher proportion of CCO.³⁸

Placental Development and Physiology

The placenta, apart from being the site of gaseous and nutrient exchange in the fetomaternal unit, is also of great importance from a cardiovascular perspective. The placenta begins to develop from as early as 6 to 7 days postconception, when the blastocyst first attaches to the uterine epithelium, having hatched from the zona pellucida.³⁹ The development of the placenta is effected by the formation of successive generations of branching villi, finger-like projections of trophoblast, which extend into the maternal blood surrounding them. This process starts between days 12 and 18 postconception⁴⁰ with the appearance of the primary villi. The appearance of connective tissue within the villi marks the transition to secondary villi, and the formation of capillaries within the villous stroma defines the transition to tertiary villi. These represent the first unit capable of providing surface area for the exchange of substances between the fetal and the maternal circulations.⁴¹ Subsequently, the trophoblast undergoes differentiation into two major lineages, the syncytiotrophoblast and the invasive trophoblast. The syncytiotrophoblast is the cell lineage responsible for the fetomaternal transfer of substances and is also the site of the endocrine functions of the placenta.^{42,43} The

Table 1-1 Study Data Regarding Percentage Distribution of Blood Flow in the Fetal Circulation

	RUDOLPH AND HEYMANN (ANIMAL STUDIES) ^{34,35}	ST. JOHN SUTTON ET AL ³⁶	RASANEN ET AL ³²	MIELKE AND BENDA ²⁶
Number of subjects	44*	38	63	Various (85-197)
RV/LV	65%	52%	53%*	59%
PBF/CCO	3.7% [†]	22%	13%*	11%
DA/RV	90%	47%	75.5% [‡]	78%

*Reference is to study by Rudolph and Heymann,³⁵ which provides the data on PBF/CCO in animal studies.

[†]Increases with gestational age.

[‡]Decreases with gestational age.

CCO, combined cardiac output; DA, ductus arteriosus; LV, left ventricle; PBF = pulmonary blood flow; RV, right ventricle.

invasive trophoblast further differentiates into interstitial and endovascular subtypes. The interstitial invasive trophoblasts are responsible for anchoring the placenta within the uterine wall, and the endovascular invasive trophoblasts invade the maternal spiral arteries, transforming them into distensible, dilated vessels, capable of delivering the increased blood flow that will be required as gestation progresses. Failure of the normal development of the invasive process has been implicated in the etiology of preeclampsia, intrauterine growth retardation, and intrauterine fetal death, although there is some controversy as to which stage of the process is responsible for which condition.⁴⁴ Nutrient and gaseous exchange takes place at the level of the chorionic villi, which contain fetal capillary loops and which are bathed in maternal blood, supplied by the spiral arteries and drained by uterine veins. Vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) are thought to play crucial roles in promoting placental angiogenesis as well as regulating placental blood flow.⁴⁵

As has been mentioned, the development of an effective placental circulation requires that the spiral arteries transform to low-resistance vessels. Under normal circumstances, the placenta is the site of the lowest resistance in the fetal circulation.³³ Studies of the pulsatility index (PI = difference between the peak systolic velocity and the minimum diastolic velocity, divided by the mean velocity) of the umbilical artery have shown that it falls at the end of the first trimester. This is thought to be due to decreasing placental resistance caused by the increased placental angiogenesis and endovascular invasive trophoblast action occurring at this time.⁴⁶ The umbilical artery PI seems to be mainly influenced by the development of trophoblastic villous structures.⁴⁷ Similarly, some fetuses with chromosomal abnormalities show increased resistance to blood flow in the umbilical artery during early pregnancy; this has been suggested to be caused by abnormal villous vascularization.⁴⁸

Animal studies have shown that the placental circulation makes up approximately 40% of CCO,³⁴ whereas noninvasive human studies estimate that the figure is slightly lower at approximately 33% and that this remains constant throughout the majority of gestation.⁴⁹ Interestingly, a study using methodology similar to that the sheep studies, performed in exteriorized human fetuses, arrived at a similar figure, approximately 30%.⁵⁰

Variability in placental anatomy and functionality are suspected in congenital heart disease, but this fascinating topic has not been extensively studied. The placenta remains a “black box” with much yet to be learned about its role in programming the cardiovascular state of its developing human partner for the remainder of life, for those with a normal, as well as a malformed heart.

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Embryology of the Cardiovascular System

Karl Degenhardt

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Hon. Charles B. Gafney.

Born in Ossipee, N. H., 1843; enlisted Sept. 27, 1862, as Second Lieutenant of Co. B, 13th New Hampshire Volunteers; promoted to First Lieutenant, June 1, 1863, and to Captain, May 30, 1865; severely wounded in the thigh at Petersburg, June 15, 1864; was Clerk to the National Senate Committee on Naval Affairs for eight years; went to Rochester, N. H., in 1871, and formed a law partnership with Joseph H. Worcester, which firm became Worcester, Gafney & Snow; was appointed Judge of Probate for Strafford county; admitted to the Society Feb. 9, 1897; died in Rochester, N. H., Jan. 25, 1898.

Mr. Andrew Athy.

Born in County Galway, Ireland, 1832; filled public offices of trust and responsibility in Worcester, Mass., almost continuously during more than thirty years; was first elected to the Common Council in 1865, and served thirteen years; represented the city in the Legislature of 1874 and 1875; was a member of the Board of Aldermen from 1881 to 1886, and a member of the commission to build the new City Hall; candidate for mayor in 1886. He was a member of the old Jackson Guards at the time of disbandment, during the Know-Nothing administration of Governor Gardner; admitted to the Society as a life member March 5, 1898; died in Worcester, Mass., May 15, 1898.

Mr. John R. Alley.

Born in Dublin, Ireland, 1822; a prominent Boston brewer; life member of the Society. His grandfather, John Alley, was at one time lord mayor of Dublin, and his father was a graduate of Cambridge University, England. Mr. Alley, our deceased associate, had warm Irish sympathies, and it has been truly said of him that few men in Boston or New England did more for the Irish cause than he. His purse and voice were always at the disposal of his fellow-countrymen in the various phases of Irish movements in this country for the past thirty years. He was an ardent lover of Ireland, and took a lively interest in her history and literature. Admitted to the Society June 24, 1897; died in Boston, Mass., June 21, 1898.

Joseph H. Fay, M. D.

A graduate of the University of Vermont; admitted to the Society March 3, 1898; died in Fall River, Mass., June 25, 1898.

Capt. John Drum.

Born in Ireland, 1840; a veteran of the Civil War; later, commissioned Lieutenant in the regular army; saw much service in campaigns against the Indians; military instructor at St. Francis Xavier's College, New York City; on the outbreak of hostilities with Spain he was a captain in the Tenth U. S. Infantry; went with his regiment to Cuba, where he met a soldier's death; admitted to the Society July 20, 1897; killed in action before Santiago de Cuba, July 1, 1898. (The date of his death is given on page [29](#) of this volume as July 2. | It should read July 1, as here stated.)

Mr. John E. Conner.

Born in Bradford, Vt., 1852; chief of police of Chicopee, Mass., 1885 to 1894 and in 1896 and 1897; city marshal of Chicopee at the time of his death; admitted to the Society June 22, 1898; died in Chicopee, Mass., Aug. 25, 1898.

Rev. Philip Grace, D. D.

Born in County Kilkenny, Ireland, 1838; ordained to the Roman Catholic priesthood at Hartford, Conn., 1862; was attached to various churches in the diocese of Providence, R. I.; was made a doctor of divinity by Pope Leo XIII; became rector of St. Mary's church, Newport, R. I., and passed away while occupying that position; admitted to the Society March 14, 1898; died in Newport, R. I., Sept. 23, 1898.

Capt. John M. Tobin.

Born in Waterford, Ireland, 1836; was commissioned First Lieutenant in the Ninth Massachusetts at outbreak of the Civil War; became Adjutant of the regiment; participated in the battles of Yorktown, Hanover Court House, Gaines' Mill, Malvern Hill, and many other engagements; was wounded at the Battle of the Wilderness; at Malvern Hill he voluntarily took command of the regiment while Adjutant, and bravely fought it from 3 P. M. until dusk, rallying and reforming the regiment under fire, and twice picking up the regimental flag—the color-bearers having been shot down—and placing it in safe hands. In 1863-'64 he was Inspector-General of a brigade in the First Division of the Fifth Corps, at Bealton, Va. He was severely wounded at the Battle of Laurel Hill, Va. For twenty-five years he was engaged as editor and publisher of weekly papers, and also did much work upon the Boston dailies. In the recent war with Spain, Captain Tobin was Quartermaster in the First Brigade, Second Division, First Army Corps; admitted to the Society Jan. 20, 1897; died in Knoxville, Tenn., December, 1898.

Hon. Patrick Walsh.

Born in Ireland, 1840; became editor and proprietor of *The Chronicle*, Augusta, Ga.; was also manager of the Southern Associated Press; in 1894 he became United States senator from Georgia; was elected mayor of Augusta, and held the office at the time of his death; admitted to the Society January 20, 1897; died in Augusta, Ga., March 19, 1899.

Col. Patrick T. Hanley.

Born in Roscommon, Ireland, 1831; was an officer in the Ninth Massachusetts regiment during the Civil War, being successively commissioned Lieutenant, Captain, Major, and Lieutenant-Colonel; took command of the regiment at the Wilderness on the fall of Colonel Guiney; prominent in Boston business circles; admitted to the Society, November 29, 1898; died in Boston, Mass., March 31, 1899.

Hon. John H. Sullivan.

Born in County Cork, Ireland, 1848; a prominent citizen of Boston, Mass.; state senator of Massachusetts; member of the Governor's Council; sinking fund commissioner of Boston; president of the Columbia Trust and Safety Deposit Company; died in East Boston, Mass., April 9, 1899.

Hon. Eli Thayer.

Born in Mendon, Mass., 1819; descended from John Alden of Mayflower fame; elected to congress from the Worcester, Mass., district in 1856; author of "A History of the Kansas Crusade;" admitted to the Society, 1898; died in Worcester, Mass., April 15, 1899.

William F. Cummings, M. D.

Born in Rutland, Vt., 1870; graduated in medicine at the University of Vermont, 1893; treasurer of the Rutland County Medical and Surgical society; admitted to the Society, August 3, 1898; died in Rutland, Vt., April 16, 1899.

Mr. Joseph J. Kelley.

Born in Ireland, 1844; served as a member of the school board of Cambridge, Mass., and in various other positions of honor in that city; member of the Massachusetts legislature; admitted to the Society, March 29, 1898; died in East Cambridge, Mass., April 29, 1899.

Mr. William Slattery.

Born in Ireland, 1849; graduated from the law school of Harvard University; became a prominent lawyer of Holyoke, Mass.; associate justice of the city court; admitted to the Society, June 23, 1898; died in Holyoke, Mass., July 22, 1899.

Rev. George W. Pepper.

Born in County Down, Ireland, 1833; was ordained to the Methodist Episcopal ministry in this country; a member of the North Ohio conference for a period of forty years; commanded a company in the Eightieth Ohio regiment during the Civil War and later served as a chaplain; in 1890 was appointed U. S. consul to Milan, Italy, by President Harrison; admitted to the Society on its organization, January 20, 1897; died in Cleveland, O., August 6, 1899.

Rev. Denis Scannell.

Born in County Kerry, Ireland, 1846; was ordained to the Roman Catholic priesthood at Alleghany, N. Y., 1870; appointed rector of St. Anne's church, Worcester, Mass., 1872, having previously had charge of the parish in Blackstone, Mass.; served two terms of three years each on the school board of Worcester; admitted to the Society, November 3, 1898; died in Worcester, Mass., August 20, 1899.

Mr. Edmund Phelan.

Born in Ireland 31 years ago; at the time of his death he was president of Newspaper Mailers' Union, No. 1, Boston, Mass. He was known throughout the state as a temperance worker in Catholic circles, and also took much interest in the work of our Historical Society. He died at his home, 32 Adams street, Roxbury (Boston), Mass., November 29, 1899.

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